PATENT/Docket No.: 20695C-003100US

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CERTIFICATE OF MAILING (37 CFR 1.8)
Date of Deposit with U.S. Postal Service: October 4, 2005

I hereby certify that this transmittal, together with the appeal brief referred to below, is being deposited with the United States Postal Service as first class mail under 37 CFR 1.8 on the date indicated above and is addressed to Mail Stop Appeal Brief - Patents, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

Karen Karlin

Karen Karlin

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS

Art Unit		1654
Examiner		Michael V. Meller
Applicant(s)	:	Heinz Redl et al.
Application No.:		09/486,516
Filed	:	June 7, 2000
For	:	FIBRINOGEN-BASED TISSUE ADHESIVE CONTAINING AN ELASTASE INHIBITOR

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF UNDER 37 CFR 1.192

Sir:

Appellants hereby transmit three (3) copies of the brief required under 37 CFR 1.192 in connection with the appeal in the above-captioned application. The NOTICE OF APPEAL UNDER 37 CFR 1.191 was filed on June 24, 2005, and received by the Patent and Trademark Office on June 27, 2005.

Appellants hereby request that the fee for filing a brief in support of an appeal, $500.00 (large entity), or such greater or lesser amount as the Commissioner may deem is required by 37 CFR 1.17(f), be charged to Deposit Account No. 20-1430.

[X] The brief is being filed under 37 CFR 1.8 and the required Certificate of Mailing appears above.

[ ] Appellants hereby request an oral hearing pursuant to 37 CFR 1.194 and hereby request that the fee for filing a request for oral hearing, $1000.00 (large entity), or such greater or lesser amount as the Commissioner may deem is required by 37 CFR 1.17(g), be charged to Deposit Account No. 20-1430.

[X] Appellants reserve the right to request an oral hearing pursuant to 37 CFR 1.194 following receipt of the Examiner's Answer.

[X] A Petition to Extend Time for two months from August 27, 2005 to October 27, 2005 is enclosed.

Respectfully submitted,

TOWNSEND and TOWNSEND and CREW LLP

Date: October 4, 2005

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Enclosures: Appellant's Brief (in triplicate)
Pet. to Extend Time SB/22 with fee authorization (in duplicate)

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AF/
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On October 4, 2005

TOWNSEND and TOWNSEND and CREW LLP

By Karen Karlin

PATENT
Attorney Docket No.: 20695C-003100US
Client Ref. No.: WM-206.00 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Heinz Redl et al.

Application No.: 09/486,516

Filed: June 7, 2000

For: FIBRINOGEN-BASED TISSUE ADHESIVE CONTAINING AN ELASTASE INHIBITOR

Customer No.: 44183

Confirmation No. 5257

Examiner: Michael V. Meller

Technology Center/Art Unit: 1654

APPELLANT'S BRIEF UNDER 37 C.F.R. § 1.192

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief is filed in triplicate pursuant to 37 C.F.R. § 1.192(a), following the Notice of Appeal, received by the PTO on June 27, 2005. A request for a two month extension of time for response, from August 27, 2005 to October 27, 2005, is submitted herewith. Also submitted in triplicate with this brief is authorization to pay the fee as set forth in 37 C.F.R. § 1.17(c). No oral hearing will be requested.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real part in interest in U.S. Application No. 09/486,516 is Baxter Aktiengesellschaft.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences known to Appellant, Appellant's legal representative, or assignees will directly affect, or be directly affected by, or have bearing on, a decision by the Board of Patent Appeals and Interferences in this pending appeal.

III. STATUS OF THE CLAIMS

Claims 29-73 were originally filed. Claims 30-32, 34-35, 43-50, 52-53, 61-69 have been canceled. Claims 29, 33, 36-42, 51, 54-60 and 70-73 are pending in the present application. In the Final Office Action mailed January 24, 2005, the Examiner has rejected claims 29, 33, 36-42, 51, 54-60 and 70-73 under 35 U.S.C. § 103(a), alleging obviousness over U.S. Patent No. 5,418,221 ("Hammarström") or U.S. Patent No. 5,631,011 ("Wadström") in view of U.S. Patent No. 5,271,939 ("Robertson") or WO 92/22309 ("Mehta") and further in view of U.S. Patent No. 5,397,694 ("Atkinson"). The claims do not stand and fall together. The dependent claims are patentable independent of the patentability of the independent claims.

IV. STATUS OF THE AMENDMENTS

No amendment was filed subsequent to the final Office Action of January 24, 2005.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention relates to a fibrinogen-based tissue adhesive comprising an elastase inhibitor selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof. The invention is formulated based on the surprising discovery that these non-

plasminogen fibrinolysis inhibitors, or the so-called "elastase inhibitors," can inhibit fibrinolysis in a manner equally effective to fibrinolysis inhibition mediated by known inhibitors of plasmin or plasminogen activator.

Claim 29

The subject matter claimed in independent claim 29 is a tissue adhesive comprising fibrinogen and an admixed elastase inhibitor, wherein the elastase inhibitor is selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof.

Claim 33

The subject matter claimed in dependent claim 33 is a tissue adhesive as set forth in claim 29, wherein the tissue adhesive is comprised of human proteins.

Claim 36

The subject matter claimed in dependent claim 36 is a tissue adhesive as set forth in claim 29, wherein the ratio in weight of said elastase inhibitor to said fibrinogen is from 1:100 to 1:150,000.

Claim 37

The subject matter claimed in dependent claim 37 is a tissue adhesive as set forth in claim 29, wherein the ratio in weight of said elastase inhibitor to said fibrinogen is from 1:500 to 1:110,000.

Claim 38

The subject matter claimed in dependent claim 38 is a tissue adhesive as set forth in claim 29, wherein said tissue adhesive contains at least 10^{-6} U of elastase inhibitor per gram of fibrinogen.

Claim 39

The subject matter claimed in dependent claim 39 is a tissue adhesive as set forth in claim 29, wherein said tissue adhesive contains from between 10^{-3} and 10 U of elastase inhibitor per gram of fibrinogen.

Claim 40

The subject matter claimed in dependent claim 40 is a tissue adhesive as set forth in claim 29, further comprising plasminogen in an amount of at least 0.0001 mg/mg of fibrinogen.

Claim 41

The subject matter claimed in dependent claim 41 is a tissue adhesive as set forth in claim 40, wherein said plasminogen is contained in an amount of at least 0.001 mg/mg of fibrinogen.

Claim 42

The subject matter claimed in dependent claim 42 is a tissue adhesive as set forth in claim 40, wherein said plasminogen is contained in an amount of more than 0.01 mg/mg of fibrinogen.

Claim 51

The subject matter claimed in dependent claim 51 is a tissue adhesive as set forth in claim 29, wherein said tissue adhesive is free from kininogenic proteins.

Claim 54

The subject matter claimed in dependent claim 54 is a tissue adhesive as set forth in claim 29, wherein said tissue adhesive is resistant to lysis in an environment with high activity for a period of time which is at least 10 hours.

Claim 55

The subject matter claimed in dependent claim 55 is a tissue adhesive as set forth in claim 29, wherein said tissue adhesive is resistant to lysis in an environment with high fibrinolytic activity for a period of time which is at least 15 hours.

Claim 56

The subject matter claimed in dependent claim 56 is a tissue adhesive as set forth in claim 29, wherein said tissue adhesive is lyophilized.

Claim 57

The subject matter claimed in dependent claim 57 is a tissue adhesive as set forth in claim 29, wherein said tissue adhesive is present in solution.

Claim 58

The subject matter claimed in dependent claim 58 is a tissue adhesive as set forth in claim 57, wherein said solution is deep-frozen.

Claim 59

The subject matter claimed in dependent claim 59 is a tissue adhesive as set forth in claim 29, wherein said tissue adhesive is present in virus-inactivated form.

Claim 60

The subject matter claimed in dependent claim 60 is a tissue adhesive as set forth in claim 29, wherein said elastase inhibitor is of recombinant origin.

Claim 70

The subject matter claimed in independent claim 70 is a method for treating wounds or hemorrhages with high fibrinolytic activity in patients, comprising administering an

effective dose of a tissue adhesive preparation containing fibrinogen and an elastase inhibitor, wherein said elastase inhibitor is selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof.

Claim 71

The subject matter claimed in dependent claim 71 is a method as set forth in claim 70, wherein said wound or hemorrhage is urological.

Claim 72

The subject matter claimed in independent claim 72 is a method for treating wounds or hemorrhages in patients, comprising administering an effective dose of a tissue adhesive containing fibrinogen and an elastase inhibitor by means of an application device.

Claim 73

The subject matter claimed in dependent claim 73 is a method as set forth in claim 72, wherein said wound or hemorrhage is urological.

VI. GROUNDS OF REJECTION TO BE REVIEWED AND APPEALED

1. The rejection for alleged obviousness is improper because absent impermissible hindsight reconstruction, there is no motivation or suggestion to combine the disclosures of the cited references. Further, Applicants have demonstrated unexpected results sufficient to rebut any alleged *prima facie* case of obviousness.

VII. ARGUMENT

A. *Prima facie* obviousness has not been established

1. The standard for a *prima facie* obviousness rejection

According to M.P.E.P. § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art references must teach or suggest all the claim limitations. *See also, In re Rouffet*, 47 USPQ2d 1453, 1459 *stating that*, "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination" (emphasis added). The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999). *See also, In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990) and *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). The teaching for suggestion to make the claimed combination must be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Examiner has maintained the rejection under 35 U.S.C. § 103(a), alleging obviousness of claims 29, 33, 36-42, 51, 54-60 and 70-73 over Hammarström or Wadström in view of Robertson or Mehta and further in view of Atkinson.

2. There exists no motivation or suggestion to combine the cited references

Applicants respectfully assert that the Examiner has not provided the requisite specific and "clear and particular" suggestion, teaching or motivation to combine the cited references in attempting to render obvious the presently claim tissue adhesives. At most, the Examiner has shown only a general motivation to combine Hammarström or Wadström in view of Robertson or Mehta. The combination of these references does not teach or suggest the

particularly claimed tissue adhesive comprising an elastase inhibitor selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof. There is no suggestion or motivation whatsoever to further combine the disclosure of Atkinson, because this reference is non-analogous art. In formulating the present rejection, the Examiner has applied impermissible hindsight reconstruction and used the teachings of Applicants' own specification to combine references disclosing disparate subject matter.

The present invention is a selection invention. Independent claims 29 and 70 are directed to a tissue adhesive and specifically set forth the Markush group that the "elastase inhibitor is selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof."

The Examiner alleges that it would have been obvious to create a tissue adhesive comprising a fibrinolysis inhibitor wherein an elastase inhibitor, such as eglin, α1-antiprotease, and mixtures thereof, is substituted for or included in addition to a plasmin inhibitor (*i.e.*, aprotinin) or a plasminogen activator inhibitor. The Examiner alleges that the use of fibrinogen in the tissue adhesives of Hammarström and Wadström is for the same purpose as the use of an elastase inhibitor in the compositions of Robertson and Mehta (wound healing, generally), and that one of skill in the art would thus be motivated to combine the ingredients for enhanced effects of the resulting composition. The Examiner alleges this is because the cited references relate generally to surgery and/or wound healing and are for the same purpose. The Examiner reasons that therefore, one of skill in the art would have a general motivation to combine the cited references. The Examiner maintains that there are not distinct types of wound healing, but that "wound healing is wound healing." *See*, Official Actions dated July 18, 2002; March 11, 2003; June 30, 2004; and January 24, 2005. Applicants cannot agree. This general motivation alleged by the Examiner is insufficient to support a proper rejection under 35 U.S.C. 103(a). *See, In re Rouffet*, 47 USPQ2d 1453, 1459, *supra*.

Hammarström and Wadström both disclose tissue adhesives containing fibrinogen and plasminogen, which are generally used for wound healing, but do not disclose or suggest any elastase inhibitors. Hammarström discloses a tissue adhesive used for joining living mineralized tissue, such as teeth or bones, or facilitating introduction of artificial implants, such as tooth

implants and artificial joints. Some embodiments of Hammarström's adhesive contain fibrinogen, Factor XIII, thrombin, and, optionally, aprotinin. Wadström discloses a tissue adhesive comprising fibrin or fibrinogen and a polymer for a desirable viscosity and reduced scar formation during wound healing.

a. Hammarström or Wadström in view of Robertson

Robertson discloses as part of an extended list of "epithelial cell health promoters," unspecified elastase inhibitors as adjuncts to wound healing, but does not disclose or suggest any tissue adhesive. Robertson does not disclose or suggest an elastase inhibitor selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof. Of the many possible elastase inhibitors Robertson could choose, none are specified.

Robertson relates to methods and compositions useful for preventing and treating corneal haze caused by exposure to laser irradiation during eye surgery. Various so-called "wound healing modulators" are used according to Robertson, which also suggests the use of elastase inhibitors as "epithelial cell health promoters" that contribute to the overall health of the eye. Elastase inhibitors were used as compounds known to contribute to the health of epithelial cells of the cornea (*see, Id.* at column 11 lines 37-44 and column 12 lines 3-15) and not for their effect of preventing fibrinolysis. Robertson's disclosure of using elastase inhibitors in the treatment of corneal haze would not suggest or motivate one of skill in the art of developing tissue adhesives to add an elastase inhibitor of any kind as an additional ingredient in a tissue adhesive composition. Because Robertson does not select any particular elastase inhibitor, Robertson's disclosure definitely does not suggest or motivate one of skill in the art of developing tissue adhesives to add an elastase inhibitor selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof as an additional ingredient in a tissue adhesive composition.

b. Hammarström or Wadström in view of Mehta

Mehta discloses the use of the elastase inhibitor, 4-(4-chlorophenyl-sulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, which is distinct from eglin, α1-antiprotease, and mixtures thereof, and also does not disclose or suggest any tissue adhesive. The use of elastase inhibitors in Mehta is also significantly different from the general purpose of using fibrinogen in a tissue adhesive. Fibrinogen is an essential component in a tissue adhesive, *e.g.*, the tissue adhesive disclosed by Wadström, for the process of thrombosis that rejoins tissue of a wound or at the site of a surgery. In this situation, premature fibrinolysis is undesirable and sought to be prevented, which is precisely why elastase inhibitors are used in the tissue adhesives of the present invention (see, *e.g.*, page 6 lines 3-12 and page 7, lines 1-17 of the present specification). On the other hand, Mehta relates to treatment of vascular diseases where dissolution of blood clots is desirable and in fact teaches the use of thrombolytic agents (see, *e.g.*, page 4 the first and second full paragraph of Mehta). The use of the elastase inhibitor, 4-(4-chlorophenyl-sulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, is thus not connected by Mehta to its property to prevent fibrinolysis. One skilled in the art would therefore not be suggested or motivated to add an elastase inhibitor selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof into his tissue adhesive upon learning the invention disclosed by Mehta.

c. Further in view of Atkinson

Atkinson discloses eglin as an elastase inhibitor, but does not directly relate to wound healing of any type. There is no suggestion or motivation to further combine the disclosure of Atkinson by the Examiner's own reasoning, because Atkinson is not even concerned with general wound healing. Atkinson is non-analogous art. Atkinson discloses the use of an elastase inhibitor, eglin, in toothpaste, mouthwash, and skin cream compositions for cosmetic and therapeutic purposes. This reference merely indicates the existence of the compound eglin and does not teach or suggest using eglin for wound healing or in a tissue adhesive. Atkinson does not disclose anything regarding the inhibition of fibrinolysis using an

elastase inhibitor, such as eglin. Atkinson further does not disclose or suggest the elastase inhibitor α1-antiprotease.

The foregoing demonstrates that, absent impermissible hindsight reconstruction by the Examiner, and the teachings of Applicants' own specification, the combined disclosures of Hammarström or Wadström with Robertson or Mehta and Atkinson do not provide the required specific and "clear and particular" suggestion, teaching or motivation to allegedly render obvious the particularly claimed tissue adhesives comprising an elastase inhibitor selected from eglin, α1-antiprotease, or mixtures thereof. Accordingly, no *prima facie* case of obviousness has been properly established.

3. The combined references do not teach or suggest the elements of the dependent claims

Regardless of whether there exists a reason to combine the disclosures of Hammarström or Wadström with Robertson or Mehta, and Atkinson, the combined disclosures of these references do not teach or suggest anything regarding the relative amounts of fibrinogen and an elastase inhibitor such as eglin, α1-antiprotease, and mixtures thereof in a tissue adhesive. The combined disclosures do not teach or suggest a tissue adhesive wherein the ratio in weight of the elastase inhibitor to fibrinogen is from 1:100 to 1:150,000, as recited in claim 36, or from 1:500 to 1:110,000, as recited in claim 37. The combined disclosures further do not teach or suggest a tissue adhesive that contains at least 10^{-6} U of elastase inhibitor per gram of fibrinogen, as recited in claim 38, or from between 10^{-3} and 10 U of elastase inhibitor per gram of fibrinogen, as recited in claim 39. Therefore, the combined disclosures of Hammarström or Wadström with Robertson or Mehta, and Atkinson do not teach or suggest the inventions of claims 36-39.

The combined disclosures of Hammarström or Wadström with Robertson or Mehta, and Atkinson further do not teach or suggest a fibrinogen-based tissue adhesive further comprising plasminogen in an amount of at least 0.0001mg/mg of fibrinogen, as recited in claim 40, or in an amount of at least 0.001mg/mg of fibrinogen as recited in claim 41, or in an

amount of more than 0.01 mg/mg of fibrinogen, as recited in claim 42. Therefore, each and every element of claims 40-42 is not taught or suggested by the combined references.

The combined disclosures of Hammarström or Wadström with Robertson or Mehta, and Atkinson further do not teach or suggest a fibrinogen-based tissue adhesive comprising an elastase inhibitor such as eglin, α1-antiprotease, and mixtures thereof that is free from kininogenic proteins (*i.e.*, kallikrein, *etc.*). Therefore, each and every element of claim 51 is not taught or suggested by the combined references.

The combined disclosures of Hammarström or Wadström with Robertson or Mehta, and Atkinson further do not teach or suggest a fibrinogen-based tissue adhesive comprising an elastase inhibitor such as eglin, α1-antiprotease, and mixtures thereof wherein the tissue adhesive is resistant to lysis for any amount of time. Atkinson does not disclose anything regarding the inhibition of fibrinolysis using an elastase inhibitor, such as eglin. Therefore, the disclosures of the combined cited references do not teach or suggest each and every element of claims 54-55.

The combined disclosures of Hammarström or Wadström with Robertson or Mehta, and Atkinson further do not teach or suggest a fibrinogen-based tissue adhesive comprising an elastase inhibitor such as eglin, α1-antiprotease, and mixtures thereof wherein the tissue adhesive is present in virus-inactivated form. Therefore, each and every element of claim 59 is not taught or suggested by the combined references.

The combined disclosures of Hammarström or Wadström with Robertson or Mehta, and Atkinson further do not teach or suggest a fibrinogen-based tissue adhesive comprising an elastase inhibitor such as eglin, α1-antiprotease, and mixtures thereof wherein the elastase inhibitor is of recombinant origin. Neither Robertson, Mehta or Atkinson teach or suggest an elastase inhibitor selected from eglin, α1-antiprotease, and mixtures thereof that is of recombinant origin. Therefore, each and every element of claim 60 is not taught or suggested by the combined references.

B. **Applicant's unexpected results rebut any alleged *prima facie* case of obviousness**

Regardless of whether a *prima facie* case of obviousness has been established, tissue adhesives of the present invention have surprising and unexpected effectiveness because, before Applicants' invention, it was a "standard practice" of those of skill in the art to include a plasmin inhibitor or a plasminogen activator inhibitor in fibrinogen-based tissue adhesives. For example, page 4, lines 6-9 of the specification states:

> "[I]t has become a rule in tissue glueing to provide for the addition of a plasmin inhibitor or a plasminogen activator inhibitor so as to inhibit the action of plasmin directly or indirectly, to thus protect the sealant, primarily in its initial phase, from a premature fibrinolysis."

The effectiveness of the present tissue adhesives are surprising and unexpected because, before the present invention, those of skill in the art did not use non-plasminogen fibrinolysis inhibitors, including elastase inhibitors, in fibrinogen based tissue adhesives. The specification at page 6, lines 3-9 states:

> "For, surprisingly, it has been shown that the fibrinolysis process cannot [sic] only be prevented by inhibiting plasmin or by inhibiting the activation of plasminogen to plasmin, but also by elastase inhibitors or by inhibitors whose fibrinolysis-inhibiting action is mainly based on a non-plasmin fibrinolysis mechanism, respectively."

It had been shown that the non-plasmin fibrinolytic pathway could not be inhibited by specific elastase-inhibiting peptides. The specification states at page 6, lines 18-23 that:

> "[Y]et, it has also been shown that this non-plasmin fibrinolytic pathway could not be inhibited by specific elastase-inhibiting peptides, such as N-methoxy-succinyl-L-alanyl-L prolyl-L valanyl chloromethyl ketone (AAPVCK), either (cf. Simon *et al.*, BLOOD 82(8) (1993), pp. 2414-2422).

Further, including an elastase inhibitor such as eglin, α1-antiprotease, and mixtures thereof, in a fibrinogen-based tissue adhesive surprisingly inhibits *in vivo* fibrinolysis comparably to plasminogen fibrinolysis inhibitors. At page 6, line 23 through page 7, line 17 and Figures 1-4 the specification teaches:

> "It was more surprising that it could be found out in the course of the present invention that inhibitors which do not have any (substantial) plasmin- or plasminogen activator-inhibiting activities, i.e. the elastase inhibitors of the invention, can ensure a very well controllable lytic process of the clot formed both in vitro and in vivo. This proved particularly suitable in tissues with increased fibrinolytic activity in which they can prevent early lysis even at moderate concentrations.
>
> Premature lysis also plays a role in tissues with high fibrinolytic activity, primarily within the first time after the sealing has been made, since premature lysis may lead to a (partial) detachment of the sealant and, thus, to rebleeding.
>
> Furthermore, it has been shown that the elastase inhibitor to be used according to the invention in the tissue adhesive exhibited its fibrinolytic activity not only in combination with conventional inhibitors acting on plasmin, but that even the entire fibrinolysis inhibition can be ensured by the elastase inhibitor alone."

Evidence of secondary considerations such as unexpected results can be used to overcome a *prima facie* case of obviousness and establish the non-obviousness of a claimed invention. *See, In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995). The Examiner states that one of skill in the art would have been motivated to combine the elements of the present invention, a fibrinogen adhesive and an elastase inhibitor selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof, as each of these components are generally used in wound healing. However, even if one of skill in the art would have been motivated to combine the elements of the present invention, the unexpected effectiveness of fibrinolysis-inhibition arising from the use of an elastase inhibitor, such as eglin, α1-antiprotease, and mixtures thereof, with a fibrinogen-based tissue adhesive is sufficient to overcome a *prima facie* case of obviousness. The unexpected effectiveness of a tissue adhesive comprising eglin or α1-antiprotease, a

non-plasmin fibrinolysis inhibitor with surprisingly comparable effectiveness, is shown in the examples and figures of the specification.

For instance, Example 1 (beginning on page 17 of the specification) demonstrates the effectiveness of eglin or α1-antiprotease in blocking fibrinolysis of a tissue adhesive clot in an *in vitro* assay. The results of Example 1 are shown in Figures 1 and 2. The legends for Figures 1 and 2, located at page 16, line 22 through page 17, line 6, read as follows:

> Fig. 1 shows the decrease of extinction corresponding to an increasing lysis of the clot
> a) fibrin adhesive without aprotinin
> b) fibrin adhesive with aprotinin (1,000 U/ml)
> c) fibrin adhesive with alpha-1 PI (0.01 0.01 U/ml)
> d) fibrin adhesive with alpha-1 PI (0.001 U/ml)
> e) fibrin adhesive with alpha-1 PI (0.0001 U/ml)
>
> Fig. 2 shows the decrease of extinction corresponding to an increasing lysis of the clot
> a) fibrin adhesive with aprotinin (1,000 U/ml)
> b) fibrin adhesive with eglin (1 µg/ml)
> c) fibrin adhesive without aprotinin

In Figure 1, the vertical axis indicates the amount of tissue adhesive clot, where a lower value indicates less fibrinolysis inhibition. Therefore, a higher value indicates more fibrinolysis inhibition. The filled bars, unfilled bars, and horizontal line-filled bars indicate the amount of clot present at time points of 0, 7.5, and 15 hours, respectively. As Figure 1 clearly indicates, when there is neither aprotinin (a plasmin inhibitor) nor α1-antiprotease (an elastase inhibitor) present in a fibrin adhesive (FA), fibrinolysis occurs at 7.5 hours and is significant at 15 hours (first group of bars from the left). When there is aprotinin (1000 U/ml) present in the FA, some protection against fibrinolysis is achieved at 7.5 and 15 hours (second group of bars from the left). When there is α1-antiprotease (0.01 U/ml) present in the FA, fibrinolysis is essentially completely blocked for at least 15 hours (the third group of bars from the left). When there is a lower level of α1-antiprotease (0.001 or 0.0001 U/ml) present in the FA, protection against fibrinolysis is comparable to that achieved by using aprotinin at 1000 U/ml (the fourth and fifth groups of bars from the left). Figure 1 shows the surprising result that 0.01 U/ml α1-

antiprotease is a more effective inhibitor of fibrinolysis than 1000 U/ml aprotinin; 0.001 and 0.0001 U/ml α1-antiprotease is an equally effective inhibitor of fibrinolysis to 1000 U/ml aprotinin.

Similarly, Figure 2 shows that the presence of eglin (at 1 ug/ml) in the FA (the middle group of bars) provides nearly complete protection against fibrinolysis for at least 15 hours, superior to the protection by FA alone (the group of bars on the right) or FA containing plasmin inhibitor aprotinin (the group of bars on the left). Again, the vertical axis indicates the amount of tissue adhesive clot, where a lower value indicates less fibrinolysis inhibition. Therefore, a higher value indicates more fibrinolysis inhibition. The results of Figure 2, like the results of Figure 1, demonstrate an unexpected effectiveness of 1 µg/ml eglin, similar to 0.01 U/ml α1-antiprotease, in inhibiting *in vitro* fibrinolysis superior to the inhibition by 1000 U/ml plasmin inhibitor aprotinin, which is traditionally used in the art. *See also*, page 18, line 21 through page 19, line 2, which teaches:

> "It has been shown that both, with ≥1 µg of eglin/ml and with ≥ 0.01 U of α_1-antiprotease/ml it is possible to prevent the lysis of the fibrin clot which occurs in the assay within 15 hours, which, on the one hand, is a hint to the central role played by the leukocyte proteases for the degradation of the fibrin clot and, on the other hand, shows the excellent effect of the inventive elastase inhibitors for preventing this lysis."

The results of Example 2 (page 19, line 3 through page 20, lines 25), which are illustrated in Figures 3 and 4, indicate the effectiveness of eglin for inhibiting fibrinolysis *in vivo* in a rabbit model. The legends for Figures 3 and 4, located on page 17, lines 7-14, read as follows:

> "Fig. 3 shows the extent of rebleeding, expressed by the increase in the weight of the pre-weighed pads, in a hyper-fibrinolytic environment, which had been induced by infusion of t-PA; and
>
> Fig. 4 shows the extent of rebleeding, expressed by the increase in the weight of pre-weighed pads, in an environment with normal fibrinolytic activity, i.e. without t-PA infusion."

In Figure 3, the vertical axis indicates the amount of blood loss after the use of tissue adhesive STIM3, which reflects the level of fibrinolysis and a lower value thus indicates more fibrinolysis inhibition. Therefore, a higher value indicates less fibrinolysis inhibition. The diagonal line-filled bars, unfilled bars, and horizontal line-filled bars indicate average blood loss in the group of animals treated with tissue adhesive (STIM3) with aprotinin (+A), STIM3 without aprotinin (-A), and STIM3 with eglin but without aprotinin (-A+Eglin), respectively. The results in Figure 3 indicate that while the presence of aprotinin alone in STIM3 can significantly reduce fibrinolysis for at least 2 hours (diagonal line-filled bars), the presence of eglin alone in STIM3 also achieves inhibition of *in vivo* fibrinolysis at a comparable level in the same time period (horizontal line-filled bars).

Figure 4 illustrates in a similar fashion that, during a period of 4 hours, the presence of eglin alone (horizontal line-filled bars) in a tissue adhesive can achieve fibrinolysis inhibition at a level comparable with the inhibition by aprotinin (diagonal line-filled bars), a plasmin inhibitor traditionally used for this purpose. Thus, the *in vivo* data of Figure 4, like the *in vivo* data of Figure 3, shows that the elastase inhibitor eglin prevents fibrinolysis at least as effectively as the traditionally used plasmin inhibitor, aprotinin.

The Examiner has repeatedly stated that the examples, including the figures, show no fibrinolysis-inhibitory effect provided by eglin or α1-antiprotease (the Office Action mailed January 24, 2005, the Office Action mailed June 30, 2004, and the Advisory Action mailed August 18, 2004). The Examiner has alleged that Figures 3 and 4 show best results when eglin is not present. Applicants respectfully assert that the Examiner's interpretation of the examples and figures is incorrect. As discussed above, Figures 1 and 2 show that in an *in vitro* assay, when 1 μg/ml eglin or 0.01 U/ml 0.01 U/ml α1-antiprotease is used in a tissue adhesive in place of aprotinin, a higher level of fibrinolysis inhibition is achieved; superior effectiveness has been demonstrated. Figures 3 and 4 show that in an *in vivo* assay, when eglin is used in place of aprotinin in a tissue adhesive, a comparable level of fibrinolysis inhibition is achieved. This conclusion is reached by comparing the diagonal line-filled bars, which indicate a tissue adhesive

with aprotinin but without eglin; the horizontal line-filled bars, which indicate a tissue adhesive with eglin but without aprotinin; and the unfilled bars, which indicate a tissue adhesive without aprotinin or eglin.

Since the results in Figures 3 and 4 show that aprotinin, a well known plasmin inhibitor traditionally used for preventing fibrinolysis in tissue adhesives, can be adequately replaced by a non-plasmin inhibitor previously unknown for this use, Applicants respectfully assert that the results are surprising and the effectiveness of the non-plasmin inhibitor so demonstrated is unexpected. In stating that the best results are achieved when eglin is not present, the Examiner has apparently mistaken the higher values in Figures 3 and 4 to mean better results.

In addition, earlier reports indicated that the non-plasmin fibrinolytic pathway can not be inhibited by specific elastase-inhibiting peptides, *see, e.g.*, Simon *et al.*, 1993, *Blood* **82**:241-4-2422 (cited in the International search report for PCT/AT98/00202). The effectiveness of eglin and α1-antiprotesase to inhibit fibrinolysis of a tissue adhesive as shown in the present application is a particularly unexpected result in view of these earlier reports.

VIII. CONCLUSION

In summary, Applicants contend that no *prima facie* obviousness has been established. Even if a case of *prima facie* obviousness were properly made, Applicants further contend that it would be rebutted by evidence that the claimed tissue adhesive is surprisingly effective, as demonstrated by the experimental data in the present specification. This result is unexpected also because publications prior to the present invention reported the inability of specific elastase-inhibiting peptides (*e.g.*, AAPVCK) to block the non-plasmin fibrinolysis.

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance.

Respectfully submitted,

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IX. CLAIMS APPENDIX

1-28. (Cancelled)

29. (Previously Presented) A tissue adhesive comprising fibrinogen and an admixed elastase inhibitor, wherein said elastase inhibitor is selected from the group consisting of eglin, αl-antiprotease, and mixtures thereof.

30-32. (Cancelled)

33. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive is comprised of human proteins.

34-35. (Canceled)

36. (Previously Presented) A tissue adhesive as set forth in claim 29, wherein the ratio in weight of said elastase inhibitor to said fibrinogen is from 1:100 to 1:150,000.

37. (Previously Presented) A tissue adhesive as set forth in claim 29, wherein the ratio in weight of said elastase inhibitor to said fibrinogen is from 1:500 to 1:110,000.

38. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive contains at least 10^{-6} U of elastase inhibitor per gram of fibrinogen.

39. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive contains from between 10^{-3} and 10 U of elastase inhibitor per gram of fibrinogen.

40. (Original) A tissue adhesive as set forth in claim 29, further comprising plasminogen in an amount of at least 0.0001 mg/mg of fibrinogen.

41. (Original) A tissue adhesive as set forth in claim 40, wherein said plasminogen is contained in an amount of at least 0.001 mg/mg of fibrinogen.

42. (Original) A tissue adhesive as set forth in claim 40, wherein said plasminogen is contained in an amount of more than 0.01 mg/mg of fibrinogen.

43-50. (Cancelled)

51. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive is free from kininogenic proteins.

52-53. (Cancelled)

54. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive is resistant to lysis in an environment with high activity for a period of time which is at least 10 hours.

55. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive is resistant to lysis in an environment with high fibrinolytic activity for a period of time which is at least 15 hours.

56. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive is lyophilized.

57. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive is present in solution.

58. (Original) A tissue adhesive as set forth in claim 57, wherein said solution is deep-frozen.

59. (Original) A tissue adhesive as set forth in claim 29, wherein said tissue adhesive is present in virus-inactivated form.

60. (Original) A tissue adhesive as set forth in claim 29, wherein said elastase inhibitor is of recombinant origin.

61-69. (Cancelled)

70. (Previously presented) A method for treating wounds or hemorrhages with high fibrinolytic activity in patients, comprising administering an effective dose of a tissue adhesive preparation containing fibrinogen and an elastase inhibitor, wherein said elastase inhibitor is selected from the group consisting of eglin, α1-antiprotease, and mixtures thereof.

71. (Original) A method as set forth in claim 70, wherein said wound or hemorrhage is urological.

72. (Original) A method for treating wounds or hemorrhages in patients, comprising administering an effective dose of a tissue adhesive containing fibrinogen and an elastase inhibitor by means of an application device.

73. (Original) A method as set forth in claim 72, wherein said wound or hemorrhage is urological.